REMARKS

Claims 1, 2 and 5 are currently pending in the application. Only claim 1 is in independent form.

Claims 1, 2 and 5 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an antibody that binds the acetylcholinesterase fragment peptide of SEQ ID No: 1 to be used for identifying production of the AChE splice variant in the brains of mice, does not enable an antibody for diagnosing central nervous system stress in animals or humans, or for identifying production of the AChE splice variant in animals other than mice.

Specifically, the Office Action has held that the use of the term "stress" or "stressed" in the specification and the claims is improper because there is no clear definition of stress in the specification. The Office Action has held that the specification does not enable the use of mouse antibody against the splice variant of AChE to diagnose central nervous system stress in humans or in any other animals beside mice. It is respectfully submitted that the antibody of the presently claimed invention was raised against the human form of AChE and was able to recognize the I4 peptide, the AChE-R isoforms both in humans and when expressed in transgenic mice or *Xenopus*, as well as the mouse AChE-R isoform. As presently claimed, the antibody is able to recognize the I4 peptide denoted by SEQ ID No:1. As defined in the sequence listing, SEQ ID No:1 refers to a sequence of human origin. Applicants previously generated transgenic mice in *Xenopus* expressing various human AChE splice variants (including hAChE-R). The work was described in Sternfeld, et al., which is enclosed herewith. The detection of the *Xenopus*-produced I4 peptide with the present antibody is shown in Figure 1 "I4 EXT." Figure 2 shows the claimed

antibody recognizing human I4 produced by the transgenic mice referred to above. Figure 3 shows the claimed antibody recognizing the native mouse AChE-R isoform, in mice subjected to stress. Most importantly, Figures 9A-H depict immunostaining of human brain sections, obtained from Alzheimer Disease patients, showing that the claimed antibody was also able to recognize the AChE-R isoform naturally produced in humans. In other words, the presently claimed antibody is not only able to recognize the I4 peptide, against which it is raised, but it is able to recognize the AChE-R isoforms in humans, as well as mice, thereby providing proof that the antibody does cross-react with other species. The presently claimed antibody is able to recognize the AChE-R in humans and in other animals. Therefore, the claimed antibody can also recognize mouse homologues and will recognize other species having a similar level of homology.

The Office Action has held that there has been no diagnosis of central nervous stress, but instead that the inventors demonstrated the expression of AChE-R variant in the hippocampi of mice forced to swim in the confined swim stress test. This statement is accurate. However, it should be noted that the Applicants and specifically Professor Soreq, are specialists in the field of central nervous system stress, have studied the cholinergic system (which is part of the central nervous system) from the molecular, physiological, and neurological prospective and have found that alterations in the expression of different variants of AChE, particularly the elevation of AChE-R, and the consequent switch from AChE-S to AChE-R is a sensor of stress. Support for such statements can be found in numerous publications that were referenced in the response submitted May 4, 2004. Additionally, a declaration is attached hereto, including full copies of the cited references attesting to the above statements and establishing that the use of AChE-R elevation as a marker for CNS stress is well known and an

acceptable parameter in the art. It is therefore reasonable to assert that since the antibody of the present invention is specific to the AChE-R isoform, and since elevation of the AChE isoform is correlated with central nervous system stress, the anti-I4 antibody of the presently claimed invention can diagnose central nervous system stress.

Additionally, the Office Action has held that the AChE-R splice variant expression is shown by Western blot in glioblastoma samples (Figure 1), labeled as stressed and non-stressed, as well as mice transfected with the glioblastoma AChE-R variant (Figure 2) but there is no known correlation or relationship between alpha-ARP and AChE-R. As specified on page 3 of the specification, Figure 1 shows the expression of AChE in human cerebrospinal fluid samples from stressed and non-stressed subjects, detected with two antibodies, one specific to the common domain AChE, which detects all form of AChE, and the antibody claimed in the present invention, the anti-ARP antibody (alpha-I4), which is specific to the AChE-R isoform. Figures 2A and B are also described on page 3 of the specification. Figure 2 depicts the detection of AChE in the brain of transgenic mice, which express human AChE variants including AChE-R. Regarding the glioblastoma samples, Example 2, described on page 19 in the specification, describes that the Applicants found intensive overexpression of AChE-R mRNA transcripts in glioblastoma tumors. It requires clarification that α-ARP was a notation used to abbreviate the word anti-ARP, wherein α is a symbol commonly used, which means anti. Thus, in the legend of Figure 1, it is stated anti-ARP antibodies, meaning alpha-I4 and anti-ARP are synonyms and are thus used herein interchangeably.

It is therefore respectfully submitted that the specification as filed provides support for the claims as pending. Further support can be found in the attached

Declaration and accordingly, reconsideration of the rejection is respectfully requested.

This amendment could not have been made earlier as the amendment corrects and further defines over the prior art in accordance with the suggestion made in the Office Action, the suggestion first being made in the outstanding Office Action. Hence, since there remain no further issues to be resolved, it is respectfully requested that the present amendment be entered.

In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance, which allowance is respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Connie Herty